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ABSTRACT

This report, a condensation of a publication titled "Laboratory Indices of Nutritional Status in Pregnancy," summarizes the effects of normal gestation on certain laboratory indices of nutritional and metabolic status in an effort to provide the clinician with normative data applicable to healthy pregnant women. The report is divided into six sections: physiologic adjustments in general, hematologic indices, electrolytes, carbohydrates and lipid metabolism, nitrogenous indices, vitamin indices, and trace elements. Numerous tables illustrate the use of indices in determining the status of pregnancy. (CM)

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Laboratory Indices of Nutritional Status in Pregnancy

SUMMARY REPORT

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Committee on Nutrition of the Mother and Preschool Child

Food and Nutrition Board

National Research Council

NATIONAL ACADEMY OF SCIENCES

Washington, D.C., 1977

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Notice: The project that is the subject of this report was approved by the Governing Board of the National Research Council whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the Committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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PREFACE

Pregnancy is characterized by extensive adjustments in maternal physiology involving a variety of metabolic processes. These characteristic changes are often reflected in altered results of laboratory tests such that values in healthy pregnant women may fall outside a "normal range" derived from studies of nonpregnant individuals. Failure to appreciate the effects of normal gestation can thus result in errors in diagnosis.

The overall purpose of this report is to summarize and highlight the effects of normal gestation on certain laboratory indices of nutritional and metabolic status and thus provide the clinician with normative data applicable to healthy pregnant women. Prepared by the Committee on Nutrition of the Mother and Preschool Child, a committee of the Food and Nutrition Board, National Research Council, National Academy of Sciences, it represents a condensation of a publication entitled *Laboratory Indices of Nutritional Status in Normal Pregnancy*. Teachers, investigators, and others interested in a more detailed consideration of the topic are referred to the full-length version available from the Printing and Publishing Office, National Academy of Sciences, 2101 Constitution Avenue, Washington, D.C. 20418.

Support for the activities of the Committee on Nutrition of the Mother and Preschool Child, including this publication and its longer companion, was provided by the Bureau of Community Health Services, Health Services Administration, Department of Health, Education, and Welfare. Additional financial assistance was provided by Ross Laboratories, Columbus, Ohio.

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PHYSIOLOGIC ADJUSTMENTS IN GENERAL

BODY WEIGHT

The magnitude and patterns of weight gain during pregnancy have been the subject of much study over many years. Nevertheless, definition of normative data is beset with great difficulty. For a number of reasons, it is not possible to determine normal values with any degree of confidence in their precision. At best, only estimates of the average pattern can be made. Moreover, in any population there will be a considerable distribution about this average.

Figure 1

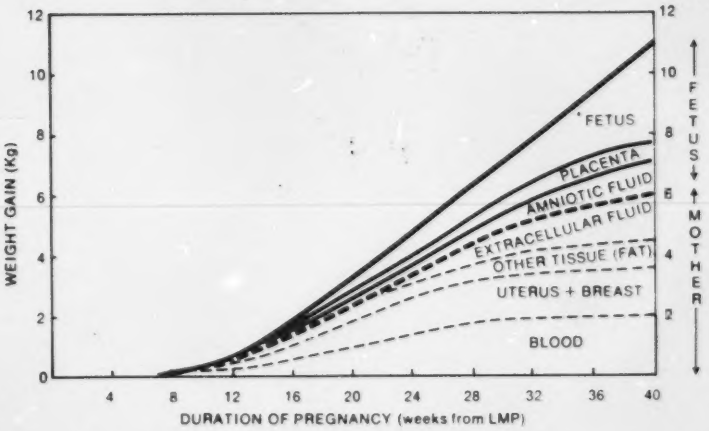

FIGURE 1 Pattern and components of cumulative gain in weight during pregnancy, assuming total gain of 11 kg. Reproduced with permission from R. M. Pitkin, Nutrition in obstetrics and gynecology, *Clin. Obstet. Gynecol.* 19:489-513, 1975.

Total weight gain during pregnancy averages about 11 kg. Customarily, there is minimal change during the early weeks following conception. Near the end of the first trimester, weight begins to accrue, and gain continues until parturition. Individual subjects exhibit considerable variability, but in general the rate of gain during the second and third trimesters is essentially linear and averages 350 to 400 g per week, as illustrated in Figure 1. Assuming a total gain of 11 kg at term, the maternal compartment

represents 6 kg and the fetal compartment 5 kg. While the overall rate of gain is similar over the last two trimesters, accumulation in maternal and fetal compartments varies with stage of pregnancy. During the second trimester, most of the gain reflects an increase of maternal components with blood volume expansion, growth of uterus and breasts, and storage of fat. By contrast, during the third trimester most of the growth involves the fetus, placenta,and amniotic fluid, while maternal tissues and fluids (except for extracellular fluid) increase to only a small degree.

Endocrine Activity

Pregnancy is associated with elaboration of peptide and steroid hormones having effects extending beyond the reproductive system.

Human chorionic gonadotropin (HCG) may be detected in the serum and urine within a few days after implantation. Serum levels increase rapidly during early pregnancy to peak values at approximately 60 days after conception. Thereafter, they decline as quickly as they rose until a relatively low level is reached which is then maintained until term. The principal reproductive effect of HCG is maintenance of the corpus luteum in early pregnancy, providing hormonal support of the developing conceptus until placental steroid production becomes sufficient. HCG has few known effects on nonreproductive tissues.

Human placental lactogen (HPL) is synthesized by the syncytiotrophoblast in progressively increased amounts during pregnancy. Its precise role in reproduction is poorly understood, but, based on its marked immunologic and biologic similarity with growth hormone, it may represent some type of growth factor for the fetus or placenta. In any event, serum levels seem to correlate with placental mass and to be lowered or raised with specific pregnancy complications. HPL appears to be a major factor in the maternal adjustments in carbohydrate and lipid metabolism.

All three classical estrogens (estrone, estradiol, and estriol) increase progressively during pregnancy. The initial source of estrogens is the corpus luteum, maintained for the early weeks after conception by HCG. Estrogen biosynthesis during the last two-thirds of gestation is a complicated process involving coordinated activities by mother, fetus, and placenta. In addition to its considerable effects on the uterus and other reproductive organs, estrogen exerts more generalized influences. It produces a rise in concentration of certain binding proteins, particularly those globulins that bind hormones, with the result that total hormone levels are elevated, while amounts of unbound (and biologically active) hormone remain essentially unchanged. Estrogen also

appears to be involved to some extent in adjustments in carbohydrate and lipid metabolism during pregnancy.

Progesterone levels rise progressively during pregnancy. The initial source is the corpus luteum, but later placental sources come to predominate. Progestational effects include relaxation of smooth muscle, not only of the genital tract but of other organs as well. Thus, the tendency toward atony of the gastrointestinal and urinary tracts appears to be a reflection of progesterone influence.

Organ Systems

A number of changes in the cardiovascular system accompany pregnancy. Pulse rate increases by an average of 15 to 20 beats per minute to a maximum in the early third trimester and falls slightly thereafter. Arterial blood pressure, particularly the diastolic component, falls through the first and second trimesters and then usually rises during the last trimester to reach the nonpregnant levels by term. The effect of pregnancy on cardiac output is a matter of some controversy, but it seems likely that the fall in late pregnancy described in earlier studies reflected inferior vena cava obstruction and that the increased level during pregnancy persists from at least midgestation until term. Venous pressure centrally and in the upper extremity is unaffected by pregnancy, while that of the lower extremity rises progressively with advancing gestation.

In respiratory function, the vital capacity is unchanged, but its components are rearranged. Tidal volume increases, mainly at the expense of expiratory reserve volume. This change, coupled with a diminished residual volume, leads to greater collapse, in effect, of the gravida's lung at the end of expiration. Gas mixing in the lung is thus more efficient. Alveolar pCO_2 falls during the luteal phase of the cycle, and this progesterone effect continues into and through pregnancy.

Renal changes of two types, anatomic and functional, accompany pregnancy. The principal anatomic effect is dilatation of the renal pelvis and ureters, typically with a right-sided preponderance. At first the mechanism was assumed to be mechanical, but this assumption was replaced by a hormonal (progesterone) theory; the bulk of recent evidence seems to favor primary mechanical causes with additive endocrine effects. Both renal plasma flow and glomerular filtration rate are elevated by as much as 50 percent throughout at least the last two-thirds of gestation. The activity of the renin-angiotensin system is greatly enhanced during pregnancy. The concentrations of renin and renin substrate are both increased severalfold. The increased angiotensin levels, which would be the anticipated result, do not, however, result in

elevation of arterial blood pressure because of the high degree of angiotensin resistance exhibited by the pregnant woman. Thus, the major physiologic consequence of increased angiotensin activity production appears to be stimulation of aldosterone secretion, which enhances tubular reabsorption of sodium and other substances from the glomerular filtrate.

The major effect of pregnancy on the alimentary tract is a generalized reduction in tone and motility of the stomach and small and large intestines, presumably a reflection of the smooth muscle-relaxing property of progesterone. As a result, gastric emptying and intestinal transit times are prolonged. Gastric acid secretion is fairly regularly reduced and the incidence of achlorhydria correspondingly increased. Liver function is generally unaffected by pregnancy, although certain "liver function tests" (e.g., a fall in serum albumin or a rise in alkaline phosphatase due to increased heat-stable enzyme from the placenta) exhibit characteristic alterations.

HEMATOLOGIC INDICES

HEMOGLOBIN-ERYTHROCYTE INDICES

Maternal blood volume increases substantially during pregnancy. The increase in plasma volume begins shortly after conception and continues until the early portion of the third trimester, when it slows and almost ceases. During the last 6 to 8 weeks of gestation, the plasma volume is approximately 50 percent greater than that of the nonpregnant condition. Erythrocyte volume, by contrast, follows a more nearly linear pattern of increase, which at term attains a level some 20 to 30 percent above the nonpregnant norm. Because of these differential patterns of increase for plasma and erythrocytes, the hemoglobin concentration, hematocrit, and erythrocyte counts decline during most of pregnancy, reaching a nadir in the early- to mid-third trimester, and rise thereafter.

The state of iron nutriture of the pregnant woman represents the principal determinant of the absolute value of hemoglobin-erythrocyte indices. In women taking iron supplements (at the recommended level of at least 30 mg of elemental iron daily), the fall in hemoglobin and hematocrit values during the last half of pregnancy exhibited by unsupplemented subjects is minimized.

Thus, supplemented patients reach term with significantly higher hemoglobin levels than do unsupplemented patients (12.3 vs. 11.1 g/dl, respectively). Moreover, the higher levels observed with iron supplementation during pregnancy persist through the puerperium.

Values for hemoglobin concentration and hematocrit from a representative longitudinal study are illustrated in Figure 2.

The reticulocyte count increases slightly during pregnancy. Erythrocyte fragility also increases, presumably reflecting the decline in serum colloid osmotic pressure.

Figure 2

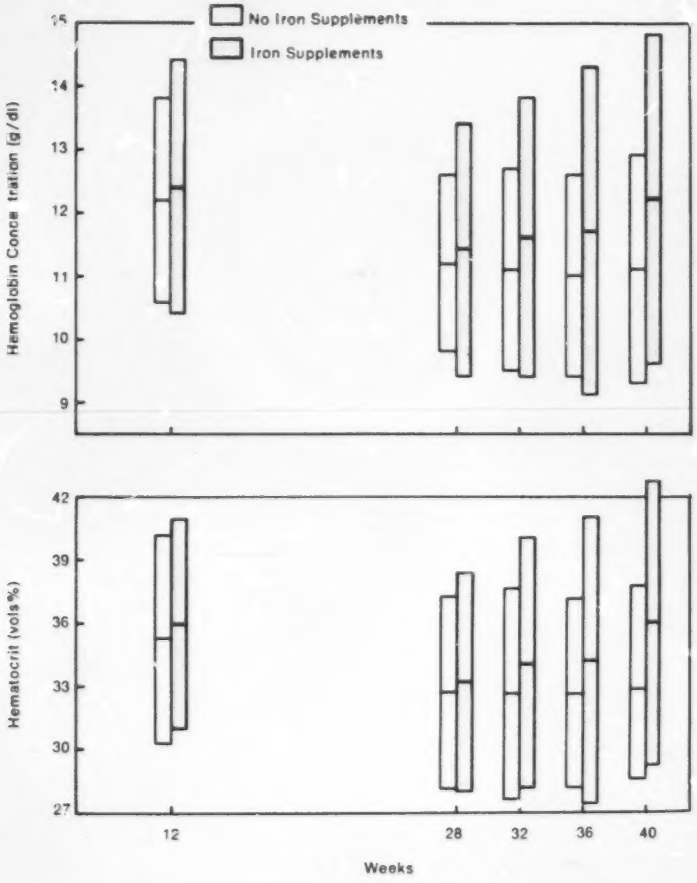

FIGURE 2 Range (mean ± 2 S.D.) of hemoglobin concentration and hematocrit during pregnancy in iron-supplemented and unsupplemented subjects. From T. Lind, personal communication, 1975.

LEUKOCYTE INDICES

As indicated in Table 1, the total leukocyte count increases during pregnancy to levels that average approximately 10,000/mm^3, the traditional upper limit of normal in nonpregnant individuals. The cell type mainly responsible for the leukocytosis of pregnancy is the neutrophil. The relative proportion of lymphocytes declines slightly, while the proportions of eosinophils, basophils, and monocytes found on differential counts remain unchanged.

Table 1

TABLE 1 Total Leukocyte Count (1,000/mm^3) [a]

	Mean	Range
Nonpregnant	7.21	4.75-9.6
First trimester	9.41	3.15-15.3
Second trimester	10.72	6.3-16.1
Third trimester	10.35	5.0-16.6

[a] From G. W. Mitchell, Jr., R. J. McRipley, R. J. Selvaraz, and A. J. Sbarra, The role of the phagocyte in host-parasite interactions, *Am. J. Obstet. Gynecol.* 96:687-695, 1966.

PLATELET AND COAGULATION INDICES

The effect of pregnancy on the platelet count is unclear. Some studies indicate an increase, others a decrease, and still others no change.

Fibrinogen levels increase progressively during gestation. Though the absolute value depends on the analytical methodology, most studies have indicated levels in late pregnancy to be 25 to 50 percent higher than nonpregnant normals. Factors VII, VIII, IX, and X all increase to varying extents with pregnancy, while prothrombin and factors V, XI, and XII are unchanged.

Bleeding, clotting, and prothrombin times are unaffected by pregnancy.

ELECTROLYTES

The pregnant woman acquires about 7 liters of extra body water, probably due to sodium retention. As would be anticipated, a relative decrease in serum osmolarity occurs as a result of a general fall in serum electrolytes. The one exception is chloride, which changes relatively little during pregnancy (Table 2). Some investigators, however, report a rise of approximately 2.5 percent

above prepregnant levels at term (not shown in table). The fact that the preterm rise is so slight probably results from the diluting effect of increased plasma volume during pregnancy. Increasing chloride levels may be a consequence of decreasing plasma bicarbonate concentrations, which would shift chloride ions out of cells into plasma and the extracellular fluid.

Table 2

TABLE 2 Alterations in Serum Bicarbonate, Chloride, Inorganic Phosphorus, Potassium and Sodium Levels during Gestation Obtained from 27 Women Followed Throughout Gestation. Ranges Are in Parentheses.[a]

Nonpregnant	1st Trimester	2d Trimester	3d Trimester
Bicarbonate (mEq/l)			
25.9 (22.0-30.0)	24.6 (22.0-27.0)	23.9 (21.5-26.5)	23.2 (20.5-26.0)
Chloride (mEq/l)			
104.7 (100.5-109.5)	102.7 (98.7-107.0)	104.2 (96.0-107.6)	104.2 (98.0-108.0)
Inorganic Phosphorus (mg/dl)			
3.04 (1.71-4.03)	3.02 (2.17-4.03)	2.76 (1.86-3.57)	2.82 (2.02-4.03)
Potassium (mEq/l)			
4.25 (3.15-5.2)	4.07 (3.15-5.2)	4.00 (3.15-4.65)	3.97 (3.15-4.45)
Sodium (mEq/l)			
143.3 (136.5-150.0)	138.9 (135.0-144.5)	139.1 (131.0-144.0)	139.5 (132.5-143.0)

[a] From R. L. Newman, Serum electrolytes in pregnancy, parturition, and puerperium, *Am. J. Obstet. Gynecol.* 10:51-55, 1957.

The lowered pCO_2 of pregnancy appears to cause a reduction in serum bicarbonate so that an appropriate pH is maintained. Thus, serum bicarbonate exhibits a slow but steady decrease throughout gestation (Table 2).

Serum phosphorus appears to decrease slightly in mid-gestation below nonpregnant values (Table 2). Recent studies suggest that there is a recovery very close to term to values similar to nonpregnant ones (not shown in table). Blood levels of potassium decrease throughout the first two-thirds of pregnancy (Table 2). Like phosphorus, potassium levels have been observed to rise slightly before term (not shown in table). Sodium levels decrease, apparently shortly after conception and vary only slightly thereafter until delivery (Table 2).

Both calcium and magnesium decrease substantially during gestation (Figure 3). The decrease in serum calcium closely parallels that of serum proteins, suggesting a decrease in the bound fraction is responsible for the diminishing total serum calcium values of pregnancy. The decrease in serum magnesium appears to reflect the increasing plasma volume of pregnancy. Some stabilization of plasma magnesium occurs during the last third of gestation; serum calcium levels tend slightly toward recovery at term.

Figure 3

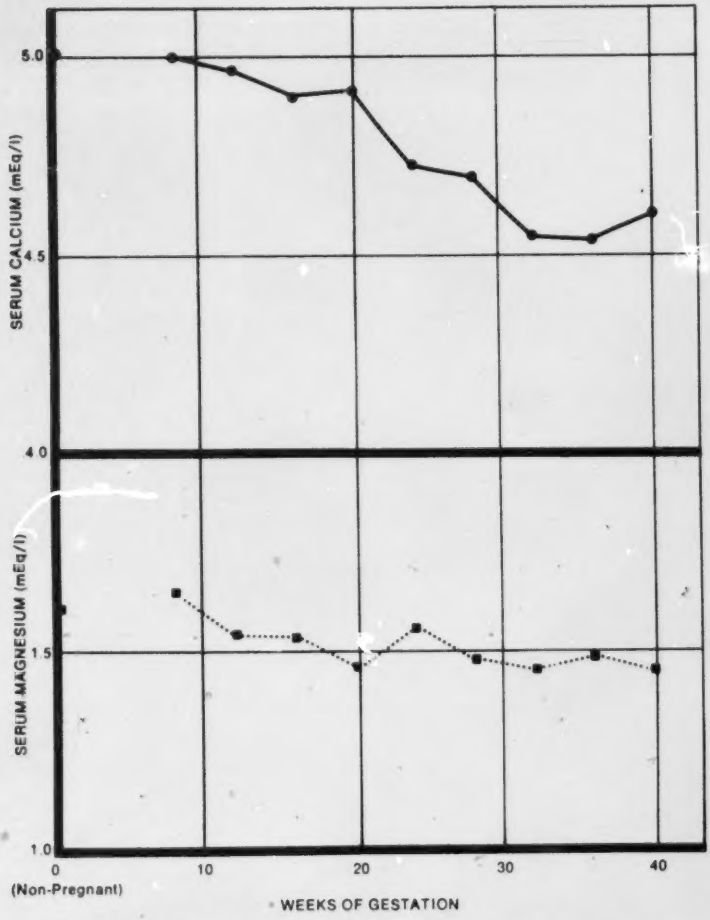

FIGURE 3 Alteration in serum calcium and magnesium levels during human pregnancy. Each point represents the mean value obtained from 100 women followed throughout the course of gestation. Adapted from C. F. Michel, Zeitschrift für Geburtschilfe and der Serum-Magnesium-Gehalt in der Schwangerschaft und Under der Geburt im Vergleich zum Serum-Kalzium, *Z. Geburtshilfe Gynäekol.* 174:276-285, 1971.

CARBOHYDRATE AND LIPID METABOLISM

CARBOHYDRATE METABOLISM

Studies of urine glucose excretion in pregnancy show that the amounts of glucose are increased five-, seven-, and eightfold over nonpregnant values, respectively, in the three trimesters of gestation. However, the variation in amount is great between individuals and within the same subject on different days.

Table 3

TABLE 3 Guide to Interpreting Glucose Measurements

1. Venous vs. capillary blood
Venous blood glucose concentrations are lower than in capillary blood. The difference is exaggerated after a glucose load and may range from 8 to 61 mg/dl higher in capillary blood.

2. Whole blood vs. plasma glucose
Whole blood glucose levels are lower than in plasma owing to the fact that red cells do not contain as much water as plasma. Interpretation of blood glucose levels is dependent upon hematocrit. (see number 6). Assuming an average pregnancy hematocrit of 35, glucose concentrations can be converted from one form to the other:
(a) Plasma glucose to whole blood glucose: $WB = P \times 0.88$.
(b) Whole blood glucose to plasma glucose: $P = WB \times 1.14$.

3. Blood collection
Blood should be collected in tubes containing an anticoagulant and sodium fluoride (2mg/ml blood) as a glycolytic inhibitor. Without this precaution, glucose will decrease 10-20 mg/dl per hour at room temperature.

4. Analytical methods
Methods that measure "true glucose" are preferable to the older methods, Folin Wu, Folin Malmros, and Hagedorn Jenson that react with nonglucose reducing substances. "True glucose" methods include:
(a) Reduction methods
(1) Somogyi-Nelson (manual)
(2) Ferricyanide method of Hoffman (autoanalyzer I)
(3) Neocuproine (autoanalyzer II including SMA 6/60 and 12/60)
(b) Enzyme methods
(1) Glucose oxidase-peroxidase system linked to an oxygen acceptor color indicator
(2) Hexokinase

5. Correlations of various methods
The Somogyi-Nelson and ferricyanide methods have seen the widest use and give nearly identical results. The neocuproine method is a few percent lower. The glucose oxidase method may run 5 to 9 percent below Somogyi-Nelson and 3 to 10 percent below the ferricyanide method. Depending on the indicator, glucose oxidase measurements may yield falsely low values due to interference from other oxygen acceptors such as ascorbic acid and uric acid.

6. Hematocrit effect
Because plasma contains a higher concentration of glucose than do red cells, a decreasing hematocrit will result in an elevation of the glucose content of whole blood; e.g., if plasma has a glucose content of 200 mg/dl, then red cells added to produce a hematocrit of 20 percent will give a blood glucose concentration of 188 mg/dl and if the hematocrit is raised to 50 percent, the blood glucose value will be 166 mg/dl.

An accurate assessment of blood glucose levels in pregnancy dictates that the physician know the various factors that may affect the laboratory studies. Some of these are outlined in Table 3. An index of blood glucose metabolism can be made by measurements of fasting levels or of levels after an oral or intravenous glucose challenge. Table 4 summarizes fasting glucose values in

normal pregnancy and demonstrates a decrease as gestation advances. The values after a 100-g oral glucose stimulation are shown in Table 5, from which it can be seen that the upper limits of normal are lower (compared with nonpregnant norms) for the fasting value and higher after 1 hour. Extensive studies (see Table 6) with the intravenous glucose tolerance curve indicate that the glucose disappearance rate (or K value) in normal pregnancies is greater than 1.13 mg/dl/min.

Measurements of hormone levels in pregnancy have shown significant changes. The fasting insulin levels become elevated by mid-gestation and continue to increase until term. The amounts of insulin released in response to a glucose stimulus are increased two- or threefold at mid- and late-pregnancy. Although the studies of blood glucagon are few in number, it would appear that the fasting values are not altered in pregnancy, but during hyperglycemia there is a greater suppression of glucagon in the pregnant woman. As a result, the insulin/glucagon ratio during pregnancy is markedly elevated with hyperglycemia. Radioimmunoassay studies of pituitary growth hormone (HGH) have been difficult since the antibody to HGH often cross-reacts with the human placental lactogen (HPL) produced by the placenta. Since HPL has growth activity, bioassays are not accurate for HGH either. The available data indicate that HGH is suppressed in pregnancy both in the basal state and after a stimulus of hypoglycemia or an intravenous arginine infusion.

Table 4

TABLE 4 Fasting Whole Blood Glucose at Various Stages in Pregnancy [a]

	Blood Glucose (mg/dl)				
	NP	1st TM	2d TM	3d TM	PP 1 week
(n)	(30)	(21)	(20)	(20)	(25)
Mean	65.9	61.3	59.1	59.6	56.1
S.E.M.	1.2	1.5	1.6	1.9	2.0
Range	52-84	50-75	45-77	44-78	40-91

[a] From F. A. Silverstone, E. Solomons, and J. Rubricius, The rapid intravenous glucose tolerance test in pregnancy, *J. Clin. Invest.* 40:2180-2189, 1961.

Table 5

TABLE 5 Tolerance to 100 Grams of Oral Glucose in 752 Randomly Selected Pregnant Subjects [a]

	Whole Blood Glucose (mg/dl)			
	Hours: 0	1	2	3
Mean ± S.D.:	69.3 ± 10.4	103.6 ± 30.8	91.7 ± 25.8	79.4 ± 24
Mean + 2 S.D.	90	165	143	127
Upper limit for normal by O'Sullivan criteria				
Whole blood (pregnancy)	90	165	145	125
Plasma (pregnancy)	103	188	165	143
Whole blood (nonpregnancy)	110	170	120	110

[a] From J. B. O'Sullivan, and C. M. Mahan, Criteria for the oral glucose tolerance test in pregnancy, *Diabetes* 13:278-285, 1964.

Table 6

TABLE 6 Intravenous Glucose Tolerance in Pregnancy (25-g Dose) Based on Actual Glucose Values [a]

	Number of Subjects	K (%/min.)				
		1st TM	2d TM	3d TM	1 wk PP	Nonpregnant
A. Normal Values: (Mean ± S.E.M.)	20-31	2.42 ± 0.14	1.92 ± 0.09	1.91 ± 0.10	1.58 ± 0.08	1.67 ± 0.08
B. Lower Limits: −2 S.D.		1.37	1.18	1.13	0.93	—

[a] From F. A. Silverstone, E. Solomons, and J. Rubricius, The rapid intravenous glucose tolerance test in pregnancy, *J. Clin. Invest.* 40:2180-2189, 1961.

LIPID METABOLISM

The methodologies for sample processing and analysis of lipids are very complex and the results can be easily altered by improper handling of the specimen. In general, it can be stated that pregnancy represents a hyperlipemic state, as all of the blood lipid fractions tend to be elevated. This can be seen in Tables 7-9, which show the patterns for total lipids, free fatty acids, triglycerides, cholesterol, and phospholipids. The lipoprotein fractions are also slightly altered and most of the changes in lipids during pregnancy are in the LDL and HDL fractions.

Tables 7

TABLE 7 Fasting Blood Levels of FFA, Glycerol and Ketones

		mM/l		
	Nonpregnant	1st TM	2d TM	3d TM
FFA (μM/l) (mean ± S.D.)	428 ± 119 [a]	413 ± 84	370 ± 147	422 ± 89
Glycerol (μM/l) (mean ± S.D.)	50 ± 17 [a]	44 ± 14	38 ± 9	50 ± 18
Acetoacetate (mM/l) (mean ± S.E.M.)	0.06 ± 0.01 [b]	—	0.15 ± 0.03	0.05 ± 0.05 [c]
β-hydroxybutyrate (mM/l) (mean ± S.E.M.)	0.10 ± 0.05 [b]	—	0.37 ± 0.04	0.09 ± 0.02 [c]

[a] From: R. G. McDonald-Gibson, M. Young, and F. E. Hytten, Changes in plasma nonesterified fatty acids and serum glycerol in pregnancy, *Br. J. Obstet. Gynaecol.* 82:460-466, 1975.

[b] P. Felig, and V. Lynch, Starvation in human pregnancy: Hypoglycemia, hypoinsulinemia, and hyperketonemia, *Science* 170:990-992, 1970.

[c] B. Persson, and N. O. Lunell, Metabolic control in diabetic pregnancy: Variations in plasma concentrations of glucose, free fatty acids, glycerol, ketone bodies, insulin, and human chorionic somatomammotropin during the last trimester, *Am. J. Obstet. Gynecol.* 122:737-745, 1975.

Table 8

TABLE 8 Serial Lipid Measurements (Mean ± S.D.) in Pregnancy (mg/dl)

	Diet	NP	Weeks Gestation 0-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36	37-40	Post-partum
Total Lipid [a]	Fed	(20) 711 ± 139	(2) 688 ± 105	(4) 653 ± 33	(8) 694 ± 148	(13) 745 ± 105	(10) 737 ± 55	(12) 900 ± 198	(9) 964 ± 208	(10) 1,018 ± 194	(8) 1,039 ± 239	(20) 711 ± 139
Triglyceride [b]	Fast	—	—	33	62	—	113	122	170	244	228	—
Cholesterol [c]	Fast	—	—	(12) 166 ± 40	(24) 175 ± 26	(16) 207 ± 21	(21) 196 ± 28	(10) 209 ± 21	(5) 209 ± 16	(9) 205 ± 27	(2) 210 ± 16	—
Phospholipid [c]	Fast	—	—	(12) 187 ± 41	(24) 203 ± 48	(12) 207 ± 38	(22) 212 ± 33	(15) 206 ± 36	(10) 231 ± 42	(9) 227 ± 33	—	—

[a] From R. R. deAlvarez, D. F. Gaiser, D. M. Simkins, E. K. Smith, and G. E. Bratvold, Serial studies of serum lipids in normal human pregnancy, *Am. J. Obstet. Gynecol.* 77:743-759, 1959.

[b] From A. Svanborg, and O. Vikrot, Plasma lipid fractions, including individual phospholipids at various stages of pregnancy, *Acta. Med. Scand.* 178:615-630, 1965.

[c] From G. O. Taylor, and E. O. Akande, Serum lipids in pregnancy and socioeconomic status, *Br. J. Obstet. Gynaecol.* 82:297-302, 1975.

Table 9

TABLE 9 Tentative Upper and Lower Limits (±2 S.D.) for Plasma Triglyceride and Cholesterol in Third Trimester Pregnancy (Mean 36 Weeks) and 6 Weeks Postpartum[a]

	Pregnant (36 weeks)		Postpartum (6 weeks)	
	LL	UL	LL	UL
Triglyceride				
Total	131	416	33	166
VLDL	55	231	4	161
LDL	31	150	13	55
DL	27	60	3	14
Cholesterol				
Total	177	345	157	227
VLDL	0	51	0	18
LDL	78	264	80	170
HDL	32	90	31	91

[a] From A. Montes, and R. H. Knopp, using methods of the Lipid Research Clinics Program, *Manual of Laboratory Operations*, National Heart and Lung Institute, Bethesda, Md., DHEW Publ. No. NIH-75-628, p. 103, 1974.

NITROGENOUS INDICES

CREATININE

Serum creatinine levels are slightly lower during pregnancy than in the nonpregnant state. During the last trimester an average value of 0.63 with a range of 0.38 to 0.89 mg/dl can be expected. Creatinine clearance nearly doubles in early gestation and by term is about 50 percent greater than in the nonpregnant woman. This marked increase probably reflects an enhanced glomerular filtration rate.

UREA

Hydration, anabolic rate, and kidney function increase in pregnancy, resulting in a decrease in blood urea nitrogen (BUN). Thus, from a nonpregnant mean of around 10.8 mg/dl, values of 7 to 8 mg/dl are usually encountered in the pregnant woman. High protein intake can increase the BUN and, correspondingly, alter total nitrogen excreted in urine. Urea clearance seems to be elevated during pregnancy.

URIC ACID

Serum uric acid levels in the nonpregnant woman range from 2.8 to 4.4 mg/dl in most studies. They quickly drop to 2.6-3.0 by the third trimester.

Uric acid excretion in the first trimester of pregnancy does not differ from the nonpregnant state. However, it tends to increase by about 50 percent during the second and third trimesters.

ENZYMES

Serum alkaline phosphatase increases progressively during pregnancy due to the secretion of a heat-stable alkaline phosphatase (HSAP) by the placenta. Since the HSAP remains constant throughout pregnancy at about 70 percent of the total alkaline phosphatase (TAP), tissues other than the placenta must also be contributing to the rise in TAP.

Serum levels of GOT (aspartate aminotransferase), GPT (alanine aminotransferase), and LDH (lactic dehydrogenase) seem to remain within the nonpregnant range during gestation. There is some indication that these enzymes may exhibit a slight continuous rise within the normal range throughout pregnancy.

AMINO ACIDS

The α-amino nitrogen is lower than in nonpregnant women. Although there is considerable variation, the levels of most amino acids in plasma are lower in the pregnant than in the nonpregnant state. Two notable exceptions are the level of arginine, which increases up to mid-gestation and then drops to below nonpregnant levels, and that of histidine, which is unchanged throughout pregnancy.

Urinary excretion rates of most amino acids are increased during pregnancy. Since amino acid concentrations vary with the menstrual cycle and are also decreased in women taking oral contraceptives, steroid hormones may play a role in regulating plasma amino acid levels.

SERUM PROTEINS

The total serum protein concentration decreases gradually during pregnancy until the twenty-eighth week, after which it remains fairly constant. This fall is due mainly to a decrease in the concentration of serum albumin.

There is a small increase in the α_1-, α_2-, and β-globulins early in pregnancy, accompanied by a slight decrease in the gamma globulins, which seems to hold constant until delivery.

Alpha$_1$-fetoprotein, derived from the fetal liver and yolk sac, can now also be measured in maternal serum. Elevated levels can be indicative of spina bifida and other central nervous system abnormalities in the fetus.

VITAMIN INDICES

Biochemical indices used to evaluate nutritional status for given vitamins are based on (a) changes in enzyme action on blood components, (b) abnormal metabolic products in blood or urine, (c) vitamin levels in blood and urine, (d) vitamin metabolites in urine, and (e) saturation or load tests of a given vitamin.

VITAMIN A

Most studies with adequate numbers have reported lower blood levels of vitamin A during pregnancy than postpartum. In a single study in which individual women were followed longitudinally, vitamin A blood levels, although they fluctuated widely, were lower during pregnancy than 6 weeks postpartum. Lower levels may reflect either the normal metabolism of pregnancy or increased demand.

Vitamin A is transported in plasma by a specific retinol-binding protein that correlates closely with plasma retinol levels. Prolonged low vitamin A intake is usually reflected in low serum levels of retinol.

VITAMIN C (ASCORBIC ACID)

Serum vitamin C levels have been found to be 10-15 percent lower during pregnancy than before. Results for postpartum values have been inconsistent across studies. These changes may reflect either an increased requirement for vitamin C or hormonal adjustments as pregnancy advances.

THIAMIN

Urinary levels of thiamin are most often used to indicate thiamin status. Decreased excretion correlates with deficiency. With normal intake, 40-90 μg of thiamin are excreted daily.

Urinary thiamin levels have been found to be low in the second and third trimester of pregnancy, with the most pronounced effects occurring during the third trimester. Values slowly return to normal postpartum. These changes may reflect depletion of thiamin by increased requirements during pregnancy.

Erythrocyte transketolase measurement is a more reliable and sensitive indicator of thiamin nutritional status than is urinary thiamin. Erythrocyte transketolase stimulation represents any enhancement in enzyme activity resulting from the *in vitro* ad-

dition of thiamin pyrophosphate expressed in percent. Erythrocyte transketolase stimulation of less than 15 percent is considered to be normal or acceptable in terms of thiamin nutriture. Values in pregnancy are generally within the normal range.

RIBOFLAVIN

Urinary excretion has been commonly used for evaluating the nutritional status for riboflavin. Dietary intake and urinary excretion of riboflavin correlate well. Urinary riboflavin levels are sensitive to recent intake, however, and hence are prone to vary considerably. This variation is reduced by the use of fasting urine samples.

During pregnancy, urinary excretion of riboflavin has been observed to be high in the second trimester and normal in the third trimester and postpartum.

Erythrocyte glutathione reductase activity provides a simple and reliable test that requires only a minute quantity of blood. Results are usually expressed in terms of activity coefficients representing the degree of stimulation resulting from the *in vitro* addition of flavin adenine dinucleotide. Activity coefficients for normal pregnant women appear to be comparable to normal nonpregnant women.

NIACIN (NICOTINIC ACID)

The usual means of assessing niacin status has been to measure urinary excretion of two major metabolites of nicotinic acid, namely, N^1-methylnicotinamide, and N^1-methyl-2-pyridone-5-carboxylamide (2-pyridone). The excretion of niacin metabolites has been observed to increase gradually during the second trimester of pregnancy, to reach a plateau during the third trimester, and to return rapidly to normal postpartum.

Recently, niacin status has been evaluated by the use of the 2-pyridone/N^1-methylnicotinamide excretion ratio. A reduction to less than 1 of the normal ratio of 1.3-4.0 indicates latent niacin deficiency. This measure requires further evaluation in pregnancy.

FOLIC ACID (FOLACIN)

Megaloblastic anemia related to folate deficiency in pregnancy occurs in a substantial number of pregnant women in developing countries and in a smaller, though still significant number in developed countries. Serum folate levels commonly fall during

pregnancy, probably in response to increased demand for the vitamin during the third trimester together with increased urinary excretion (Table 10). Folic acid supplementation usually results in a prompt increase in serum folate values (Table 10).

Table 10

TABLE 10 Serum Plasma and Erythrocyte Folic Acid by Stage of Pregnancy, including Response to Folate Supplementation in Three Studies (Numbers in Parentheses)

Test	Nonpregnant	Pregnant Trimester 1	2	3	Postpartum	References
Serum or plasma folic acid (ng/ml)						
No folate supplement						
mean		5.1 (101)	4.5 (101)	4.5 (101)	—	a
range	5-20					
200 μg/day folate supplement						
mean	—	6.6 (105)	6.7 (105)	6.3 (105)	—	a
Erythrocyte folic acid (ng/ml)						
No folate supplement						
mean	165 (31)	157 (101)	139 (101)	118 (101)	—	a
200 mμ/day folate supplement						
mean	—	165 (105)	190 (105)	187 (105)	—	a
No folate supplement						
mean ± S.E.	—	—	145 ± 16 (26)	111 ± 12 (26)	113 ± 11 (26)	b
200 mμ/day folate supplement						
mean ± S.E.	—	—	145 ± 12 (25)	185 ± 36 (25)	181 ± 16 (25)	b

a I. Chanarin, D. Rothman, A. Ward, and J. Perry, Folate status and requirement in pregnancy, *Br. Med. J.* 2:390-394, 1968.

b L. Iyengar, Folic acid requirements of Indian pregnant women, *Am. J. Obstet. Gynecol.* 111:13-16, 1971.

Serum folate level is a poor indicator of folacin deficiency; low levels may reflect recent dietary intake and not tissue reserves. Thus, a low serum folate level may not be associated with megaloblastic anemia or abnormal biochemical changes.

Erythrocyte folate level is a more accurate and less variable index of folacin nutritional status during pregnancy than serum folate and correlates well with response to folic acid supplementation (Table 10). A low erythrocyte level is slower to develop than a low serum level and, taken alone, does not distinguish between the megaloblastic anemias of vitamin B_{12} deficiency and folacin deficiency. Low folate values for both serum and erythrocytes, however, are strong evidence for folacin deficiency.

VITAMIN B_6 (PYRIDOXINE)

Plasma levels of vitamin B_6 and pyridoxal phosphate decline progressively during pregnancy, and following a tryptophan load test increased amounts of tryptophan metabolites are excreted in the urine. (Xanthurenic acid is the easiest tryptophan metabolite

to measure.) Both plasma levels and excretion are restored to normal by dietary supplementation.

Although the tryptophan load test is relatively easy to perform and has been widely used to evaluate vitamin B_6 status, the results of the test should be interpreted with care in view of the interrelated metabolic and hormonal factors involved in tryptophan metabolism.

Erythrocyte aspartate aminotransferase (EGOT) measurements can indicate depletion of vitamin B_6 reserves. Although individual variation is marked, the *in vitro* stimulation of EGOT by pyridoxal phosphate in normal subjects is usually less than 60 percent. A stimulation of over 100 percent may be encountered in vitamin B_6-depleted subjects. Additional studies are needed to establish the validity and usefulness of these guidelines in evaluating vitamin B_6 status in pregnancy.

Table 11

TABLE 11 Serum and Erythrocyte B_{12} Levels by Stage of Pregnancy in Selected Studies (Numbers in Parentheses)

Test		Nonpregnant	Pregnant Trimester 1	2	3	Postpartum	References
Serum vitamin B_{12} (pg/ml)	mean	214-1150 (range)	420 (117)	360 (117)	310 (117)	475 (117)	[a]
	mean ± S.D.	—	224 ± 115 (320)	—	182 ± 96 (119)	—	[b]
	mean	—	267 (24)	260 (37)	190 (26)	433 (24)	[c]
	mean ± S.D.	—	—	—	267 ± 111 (326)	—	[d]
	mean ± S.D.	—	—	—	293 ± 109 (53)	—	[d]
	mean ± S.D.	—	—	—	219 ± 105 (26)	—	[d]
Erythrocyte vitamin B_{12} (pg/ml)	mean ± S.D.	155 ± 35 (?N)	—	133 ± 20 (13)		—	[e]

[a] J. Metz, H. Festenstein, and P. Welch, Effect of folic acid and vitamin B_{12} nutrition in pregnancy, *Am. J. Clin. Nutr.* 16:472-479, 1965.

[b] P. D. Roberts, H. James, A. Petrie, J. O. Morgan, and A. V. Hoffbrand, Vitamin B_{12} status in pregnancy among immigrants to Britain, *Br. Med. J.* 3:67-72, 1973.

[c] R. Green, N. Colman, and J. Metz, Comparison of results of microbiologic and radioisotopic assays for serum vitamin B_{12} during pregnancy, *Am. J. Obstet. Gynecol.* 122:21-24, 1975.

[d] B. M. Hibbard, and E. D. Hibbard, Anaemia and folate status in late pregnancy in a mixed Asiatic population. *J. Obstet. Gynaecol. Br. Commonw.* 79:584-591, 1972.

[e] R. J. Harrison, Erythrocyte vitamin B_{12} levels in pregnancy, *J. Obstet. Gynaecol. Br. Commonw.* 79:226-227, 1972.

VITAMIN B_{12}

Serum vitamin B_{12} levels have been observed to fall markedly during pregnancy and to return to normal within 6 weeks postpartum (Table 11). Vitamin B_{12} supplementation apparently does not change this pattern. However, the fall does not occur in women with low initial serum vitamin B_{12} levels. Erythrocyte vitamin B_{12} levels also tend to be subnormal in pregnant women. These changes may reflect a change in vitamin B_{12} metabolism during pregnancy, and in some instances, inadequate folate nutrition. Depletion of maternal vitamin B_{12} stores cannot be discounted, however; erythrocyte concentration and muscle stores of the vitamin in late pregnancy have been shown to be correlated.

A Schilling test can distinguish among abnormal B_{12} status owed to a lack of intrinsic factor, to another form of malabsorption, or to a nutritional deficiency of vitamin B_{12}.

VITAMIN D

Methods for assessing vitamin D status have been unsatisfactory and knowledge of the metabolism of the vitamin during pregnancies conjectural. Serum levels of 25-hydroxycholecalciferol, the principal circulating metabolite of vitamin D, remain relatively constant through normal pregnancy. However, seasonal effects have been reported. Infants born of mothers with low serum concentrations of 25-hydroxycholecalciferol are likely to have low concentrations.

Serum alkaline phosphatase increases during pregnancy, particularly during the third trimester, because of the production of a heat-stable placental alkaline phosphatase.

VITAMIN E

Vitamin E status can be assessed from tocopherol levels in plasma or serum or, more indirectly, from erythrocyte hemolysis tests. During the second trimester of pregnancy, the serum tocopherol level may rise an average of 40-50 percent and return to normal postpartum. Although these changes seem to reflect changes in lipid transport, low dietary intakes of vitamin E have been associated with low plasma tocopherol levels. Plasma vitamin E levels in mothers correlate with levels both in newborn infants and in cord blood.

VITAMIN K

Dietary deficiency of vitamin K uncomplicated by other factors is rare. A deficiency most commonly occurs in situations in which there is malabsorption of fat-soluble materials or, if prolonged, antibiotic therapy has altered the gut bacterial flora.

A prolonged prothrombin time results because of decreased activities of factor VII and prothrombin. Factor IX level is also decreased, and a prolonged partial thromboplastin time occurs. In order to distinguish vitamin K deficiency from the causes of prolonged prothrombin and partial thromboplastin times, specific factor assays may be done. The simplest confirmation of vitamin K deficiency, however, is the rapid return of an abnormal prothrombin time to normal when vitamin K is given parenterally.

PANTOTHENIC ACID

The limited data available indicate that pantothenic acid levels in blood fall during pregnancy and slowly return to normal postpartum. Since most of the pantothenic acid in blood is present in the erythrocyte, any changes in hematocrit may influence pantothenic acid levels.

TRACE ELEMENTS

IRON

The most practical and widely used tests for evaluation of iron status are serum iron, total iron binding capacity, and percent saturation of transferrin. Serum iron falls as pregnancy proceeds (Table 12). This drop in serum iron levels is not a "dilutional" phenomenon; the physiologic rise in plasma volume is independent of falling iron levels. In most studies of unsupplemented women, the slope of falling iron levels increases after 20 weeks gestation which suggests that the need for iron increases as the fetus matures.

Total iron binding capacity (TIBC) rises in pregnancy (Table 12), and the elevation is directly related to length of gestation. This rise in TIBC is presumed to be an estrogen-related effect and, in small preliminary studies, has been statistically correlated with infant weight. TIBC will also rise in developing iron deficiency.

Because the mean serum iron usually falls in normal pregnancy and the mean TIBC rises, it was initially thought that these parameters would be inaccurate as diagnostic tests of iron deficiency. However, investigations suggest that the serum iron is diagnostic of iron deficiency in pregnancy if: (1) its value is 50 μg/100 ml or less in the fasting state in the absence of acute or chronic urinary tract infection or other chronic disease and (2) it relates to total iron binding capacity (TIBC) to produce a percent saturation of 15 percent or less.

Fasting serum iron values are obtained 24 hours after ingestion of any oral pharmacologic dose of iron, in the absence of parenteral iron administration, and in the morning without breakfast. It is probable that a fasting serum iron between 20 and 70 μg/dl in pregnancy might also indicate iron deficiency (not necessarily iron deficiency anemia) based on some marrow studies, and especially if the iron value relates to the TIBC to give a percent saturation of 15 or less.

ZINC

The plasma zinc concentration is currently the most widely used and accepted biochemical index of zinc nutritional status. The generally accepted normal mean lies between 80 and 100 μg/100 ml for nonpregnant women; values for serum zinc may be 5-15 percent higher. Literature data for plasma (or serum) zinc levels during pregnancy are scanty, but the few data available for pregnant women show a consistent decline in mean values from the tenth week of gestation onwards when compared with nonpregnant women (Table 12). The lower limits of normal during late pregnancy have not been identified, but a provisional level of 45-50 μg/100 ml is suggested.

Normal hair zinc levels are dependent on adequate dietary zinc intake and are depressed in human zinc deficiency. Normal hair zinc levels for pregnant women seem to be the same as for nonpregnant women and for young adult men (no sex differences have been observed). It is recommended that any individual value below 100 μg zinc/g of hair be considered suggestive of inadequate zinc nutrition.

Because the 24-hour urine zinc excretion rate is depressed only in severe zinc deficiency, this is not a sensitive index of zinc nutritional status. The normal daily urinary zinc excretion varies from 100 to 1,000 μg/24 hours. Values for pregnant women fall within this range. It is suggested that any value below 100 μg zinc/24 hours during pregnancy is abnormally low, and rates between 100 and 150 μg zinc/24 hours should be considered "borderline."

Table 12

TABLE 12 Iron, Zinc, Copper, Ceruloplasmin, and Iodine Indices in Pregnancy[a]

	Nonpregnant	Pregnant			
		Early	Mid	Late	References
Iron[b]					
serum, μg/dl					
nonsupplemented	86.6 ± 7.9	117.0 ± 7.1	80.8 ± 5.9	65.3 ± 5.5	c|c|
supplemented	110.2 ± 7.5	125.5 ± 5.4	109.3 ± 6.5	112.4 ± 8.9	
binding capacity, μg/dl					
nonsupplemented	346.0 ± 11.9	382.0 ± 9.3	461.2 ± 17.6	505.1 ± 19.3	c|c|
supplemented	300.2 ± 8.9	352.5 ± 8.9	409.9 ± 11.0	458.5 ± 13.7	
percent saturation, %					
nonsupplemented	26.0 ± 2.5	31.1 ± 2.1	17.8 ± 1.2	13.2 ± 1.2	c|c|
supplemented	38.5 ± 3.4	35.8 ± 1.9	27.2 ± 1.8	25.4 ± 2.1	
Zinc					
plasma, μg/dl	88 ± 8	68 ± 9		56 ± 9	d|d|
hair, μg/g	180 ± 37	171 ± 22	—	156 ± 27	
Copper					
serum, μg/dl	128 ± 12	195 ± 41	239 ± 46	261 ± 74	e|
Ceruloplasmin					
serum, mg/dl	34 ± 4	—	—	84 ± 15	f|
Iodine					
urine, μg/day	150	—	146	146	g,h|i|
serum TBG μg/dl	22		56	56	
plasma total thyroxine μg/dl	8.9 ± 1.5	11.8 ± 1.8	12.8 ± 2.4	13.1 ± 2.0	j|
plasma free thyroxine ng/dl	1.6 ± 0.3	1.7 ± 0.3	1.7 ± 0.3	1.6 ± 0.3	j|

[a] Iron values are mean ± S.E.M.; all others mean ± S.D.

[b] Iron nonpregnant values are from postpartum patients.

B. Svanberg, B. Arvidsson, A. Norrby, G. Rybo, and L. Solvell, Absorption of supplemental iron during pregnancy—A longitudinal study with repeated bone-marrow studies and absorption measurements, *Acta Obstet. Gynaecol. Scand.*, Supplement 48:87-108, 1975.

[d] K. M. Hambridge, and W. Droegemueller, Changes in plasma and hair concentrations of zinc, copper, chromium, and manganese during pregnancy, *Obstet. Gynecol.* 44:666-672, 1974.

[e] J. A. O'Leary, G. S. Novalis, and G. J. Vasburgh, Maternal serum copper concentrations in normal and abnormal gestations, *Obstet. Gynecol.* 28:112-117, 1966.

[f] H. Markowitz, C. J. Gubler, J. P. Mahoney, G. E. Cartwright, and M. M. Wintrobe, Studies on copper metabolism, XIV: Copper, ceruloplasmin and oxidase activity in sera of normal human subjects, pregnant women, and patients with infection, hepatolenticular degeneration and the nephratic syndrome, *J. Clin. Invest.* 34:1498-1508, 1955.

[g] D. S. Riggs, Quantitative aspects of iodine metabolism in man, *Pharmacol. Rev.* 4:284-370, 1952.

[h] H. J. Dworkin, J. A. Jacquez, and W. H. Beierwaltes, Relationship of iodine ingestion to iodine excretion in pregnancy, *J. Clin. Endocrinol. Metab.* 26:1329-1342, 1966.

[i] E. B. Man, W. A. Reid, A. E. Hellegers, and W. S. Jones, Thyroid function in human pregnancy, III: Serum thyroxine-binding prealbumin (TBPA) and thyroxine-binding globulin (TBG) of pregnant women aged 14 through 43 years. *Am. J. Obstet. Gynecol.* 103:338-347, 1969.

[j] J. A. Souma, D. C. Niejadlik, S. Cottrell, and S. Rankel, Comparison of thyroid function in each trimester of pregnancy with the use of triiodothyronine uptake, thyroxine iodine, free thyroxine, and free thyroxine index, *Am. J. Obstet. Gynecol.* 116:905-910, 1973.

COPPER

In nonpregnant subjects, documentation of low levels of serum copper or ceruloplasmin provides confirmatory evidence of copper depletion.

An increase in serum copper levels during pregnancy has been a consistent finding, but the magnitude of this increase varies considerably. Generally, a substantial increase has been observed by the second month of pregnancy, followed by a steady increase until term, with values returning to nonpregnant levels by 1 to 3 months postpartum (Table 12).

Relatively low serum copper levels for any particular stage of gestation have been observed in association with placental insufficiency and intrauterine death. Indeed, serum copper levels may be of prognostic value in cases of threatened abortion.

The few reports of serum ceruloplasmin levels during pregnancy show that a consistent increase occurs, but these data are too inadequate and too variable for a definition of a normal range at any stage of gestation.

IODINE

The most widely used biochemical index of iodine nutritional status is the 24-hour urine iodine excretion rate or the urine iodine: creatinine ratio. In nonpregnant subjects, a urine iodine excretion of less than 40 μg/24 hours is suggestive of iodine deficiency; a similar standard is suggested for pregnant women. Tests of thyroid function (thyroxine binding capacity, total thyroxine, and free thyroxine) are altered during pregnancy (Table 12). There is an increase in thyroxine binding capacity and total thyroxine; free thyroxine is maintained within the lower limits of the normal nonpregnant range.

OTHER TRACE ELEMENTS

Other trace elements of recognized nutritional importance in animals or man include: chromium, manganese, molybdenum, selenium, cobalt, fluorine, nickel, silicon, vanadium, and tin. Useful biochemical indices for these elements have not been established.